

EPO - Munich
21

22. Jan. 2009

Notice of opposition to a European patent

I. Patent opposed

Patent No.

EP-B1 1 373 529

Application No.

EP 02 702 181.5

Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)

April 23, 2008

Title of the invention

Tau-opathy model

II. Proprietor of the patent

first named in the patent specification

NV reMynd

Opponent's or representative's reference
(max. 15 keystrokes)

FRX13125OP

III. Opponent

Name

FoldRx Pharmaceuticals, Inc.

Address

300 Technology Square, 5th Floor
Cambridge, MA 02139

State of residence or of principal place of business

USA

Nationality

US

Telephone/Fax

Multiple opponents
(see additional sheet)

☐

IV. Authorisation

1. Representative

(name only one representative or name of association of representatives to whom notification is to be made)

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Additional representative(s)
on additional sheet/see authorisation

☒

Opponent's reference

FRX13125OP

2. Name(s) of employee(s) of the opponent authorised to act in these opposition proceedings under Art. 133(3) EPC

Authorisation(s) to 1./2. not considered necessary

X

has/have been registered under No.

is/are enclosed

V. Opposition is filed against

• the patent as a whole

X

• claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

• it is not new (Art. 52(1); Art. 54 EPC)

X

• it does not involve an inventive step (Art. 52(1); Art. 56 EPC)

X

• patentability is excluded on other grounds, i.e. Article

Art.

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC).

X

(c) the subject-matter of the patent opposed extends beyond the content of the application/of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC).

X

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith on a separate sheet (annex 1)

X

VIII. Other requests:

Oral Proceedings pursuant to Art. 116(1) EPC are requested in case the Opposition Division does not revoke the opposed patent on the basis of our written submission.

Opponent's reference

FRX13125OP

IX. Evidence presented

Evidence

is enclosed

☒

will be filed at a later date

7

A. Publications:

1

Particular relevance (page, column, line, fig.):

Documents D1-D30 (see pages 2-4 of our opposition brief)

2

Particular relevance (page, column, line, fig.):

3

Particular relevance (page, column, line, fig.):

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4

Particular relevance (page, column, line, fig.):

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5

Particular relevance (page, column, line, fig.):

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6

Particular relevance (page, column, line, fig.):

Continued on additional sheet

7

B. Other evidence

Continued on additional sheet

7

Opponent's reference	
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FRX131250P

X. Payment of the opposition fee is made

• as indicated in the enclosed voucher for payment of fees and costs (EPO Form 1010)

☐

• via EPO Online Services

☒

XI. List of documents

Enclosure No.

0 Form for notice of opposition

☒

1 Facts (see VII.)

☒

2 Copies of documents presented as evidence (see IX.)

a Publications

☒

b Other documents

☐

3 Signed authorisation(s) (see IV.)

☐

4 Voucher for payment of fees and costs (see X.)

☒

5 Additional sheet(s)

☒

Number of sheets

1

6 Other

☒

Please specify here:

Copy of the application as filed

Copy of the priority document

XII. Signature of opponent or representative

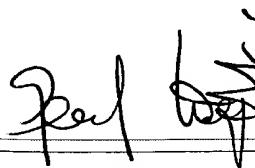
Place

Munich

Date

January 22, 2009

Signature



Name (block capitals)

Dr. Gerhard Weinzierl

In case of legal persons, signatory's position within company

European Patent Attorney

Opponent's reference

FRX13125OP

Opposition against European patent EP 1 373 529
Title: TAU-OPATHY MODEL
Proprietor: NV reMynd
Opponent: FoldRx Pharmaceuticals, Inc.
Our Ref.: FRX13125OP

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January 22, 2009

Opposition against European patent EP 1 373 529 (Application No. 02 702 181.5)

Title: TAU-OPATHY MODEL
Proprietor: NV reMynd
Opponent: FoldRx Pharmaceuticals, Inc.
Our Ref.: FRX13125OP

Patents
Trademarks
Designs

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we herewith file **Opposition** pursuant to Article 99(1) EPC against

European Patent No. 1 373 529
(European Appl. No. 02 702 181.5)
Publication and mention of the grant:
April 23, 2008

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Title of the patent:

Tau-opathy model

Proprietor:

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3000 Leuven
Belgium

The opposition fee in the amount of EUR 670.- has been paid via the EPO's online payment system. A copy of the payment receipt is attached.

I. EXTENT OF THE OPPOSITION AND REQUESTS

1. The opposition is directed against all claims of the European patent EP 1 373 529 B1 (hereinafter referred to as "the opposed patent") and is based on the grounds of Articles 100(a), (b) and (c) EPC, in particular on the grounds that
 - (1) the subject matter of the opposed patent is not novel (Article 100(a) in conjunction with Article 54 EPC);
 - (2) the subject matter of the opposed patent is not based on an inventive step (Article 100(a) in conjunction with Article 56 EPC);
 - (3) the subject matter of the opposed patent is not sufficiently disclosed (Article 100(b) in conjunction with Article 83 EPC); and
 - (4) the subject matter of the opposed patent extends beyond the content of the application as filed (Article 100(c) in conjunction with Article 123(2) EPC).
2. It is requested that the opposed patent be revoked in its entirety pursuant to Article 101(2) EPC.
3. Oral proceedings are requested in accordance with Article 116(1) EPC in the event that the Opposition Division does not consider the above requests justified on the basis of our written submissions.

II. THE DOCUMENTS RELIED UPON IN THE OPPOSITION

The priority date of the opposed patent is February 26, 2001. However, the claimed subject matter is not entitled to the priority date for the reasons provided in section VI, below. Thus, the earliest filing date of the opposed patent is its PCT filing date on February 25, 2002. Accordingly, in our opposition we rely upon the following documents:

Doc. No.	Publication No./Inventor/Applicant	Publication Date	Application Date	Priority Date
D1	Song <i>et al.</i> , <i>Neuroscience Letters</i> , 282 :65-68	March 2000	N/A	N/A
D2	Zhou <i>et al.</i> , <i>Molecular Cell</i> , 6:873-883	October 2000	N/A	N/A
D3	US 5,994,084	November 30, 1999	August 1, 1994	August 12, 1993
D4	WO 01/02552	January 11, 2001	June 30, 2000	July 2, 1999
D5	US 5,952,217	September 14, 1999	September 23, 1997	

D6	US 5,958,721	September 28, 1999	December 14, 1995	
D7	Geyskens <i>et al.</i> , <i>NATO Science Series</i> , A316:117-126	2000	N/A	N/A
D8	Escher <i>et al.</i> , <i>Chimia</i> , 54:171-173	2000	N/A	N/A
D9	Billingsley <i>et al.</i> , <i>Biochem. J.</i> , 323:577-591	1997	N/A	N/A
D10	US 6,071,694	June 6, 2000	June 5, 1995	March 2, 1993
D11	US 5,492,812	February 20, 1996	November 30, 1993	August 1, 1991
D12	WO 93/03369	February 18, 1993	August 3, 1992	August 1, 1991
D13	Mawal-Dewan <i>et al.</i> , <i>J. Biol. Chem.</i> , 27:19705-19709	September 25, 1992	N/A	N/A
D14 ¹	WO 02/065136	August 22, 2002	February 15, 2002	February 15, 2001
D14a	US 60/269,157	N/A	February 15, 2001	February 15, 2001
D15	Cafferty, Master's Thesis, "Characterization of glycogen synthase kinase 3 beta and tau interaction"	August 2000	N/A	N/A
D16	WO 99/62548	December 9, 1999	May 28, 1999	June 1, 1998
D17 ²	WO 02/35237	May 2, 2002	October 22, 2001	October 24, 2000
D17a	IT2000RM00561 (English translation thereof)	N/A	October 24, 2000	October 24, 2000
D18	Lindquist, Grant No. 1R21NS044829-01 (Abstract)	2001/2002	N/A	N/A
D19	Liu and Lindquist, <i>Nature</i> , 400:573-578	August 5, 1999	N/A	N/A
D20	Puziss <i>et al.</i> , <i>Molecular and Cellular Biology</i> , 14:831-839	January 1994	N/A	N/A
D21	Woods, Y.L. <i>et al.</i> , <i>Biochem. J.</i> 355:609-615	May 2001	N/A	N/A
D22	Thevelein J.M., <i>Yeast</i> , 10:1753-1790;	1994	N/A	N/A
D23	Crauwels <i>et al.</i> , <i>Microbiol.</i> , 1997; 143:2627-2637	1997	N/A	N/A

¹ **D14** validly entered the regional phase. It is prior art pursuant to Article 54(3) EPC.

² **D17** validly entered the regional phase. It is prior art pursuant to Article 54(3) EPC.

D24	Hartley A.D. <i>et al.</i> , <i>Genetics</i> , 136:465-474	1994	N/A	N/A
D25	Yan <i>et al.</i> , <i>Yeast</i> , 18(S1):S273	2001	N/A	N/A
D26	Zhang, Z. <i>et al.</i> , <i>Mol. Biol. Cell.</i> , 12:699-710 (2001)	August 2001	N/A	N/A
D27	Andoh <i>et al.</i> , <i>Mol. Cell. Biol.</i> , 20(18):6712-6720	2000	N/A	N/A
D28	Huang <i>et al.</i> , <i>Proc. Natl. Acad. Sci. USA</i> 96(25):14445-14450	1999	N/A	N/A
D29	Baumann <i>et al.</i> , <i>FEBS Lett.</i> , 336(3):417-424	1993	N/A	N/A
D30	Yamaguchi <i>et al.</i> , <i>Acta Neuropathol.</i> , 92(3):232-241	1996	N/A	N/A

Documents **D1-D8** were cited during the International phase.

Documents **D8-D11** were cited during the prosecution of the related U.S. application.

Documents **D12-D30** are cited by the Opponent. It is noted that **D9** and **D21-D26** were also cited in the opposed patent. Documents not specifically relied on in the arguments below evidence the state of the art at the time of the filing of the patent application that matured into the opposed patent and are provided to assist the Opposition Division in reviewing the patentability of the claims of the opposed patent.

III. THE OPPOSED PATENT

The opposed patent EP-B1 1 373 529 is based on EP Appl. No. 02 702 181.5 that has a filing date of February 25, 2002. The opposed patent claims priority from GB 0104685.3 which was filed on February 26, 2001. The mention of grant of the opposed patent was published on April 23, 2008.

The Opponent submits herewith copies of the original application ("OA") and the priority document ("PD") for the Opposition Division's and the Proprietor's convenience.

IV. THE ALLEGED INVENTION AND CLAIMED SUBJECT MATTER OF THE OPPOSED PATENT

1. The alleged invention concerns a yeast model for aspects of neurodegenerative disorders such as Alzheimer's disease. Alzheimer's disease is a neurodegenerative disorder characterized histopathologically by the loss of synapses and finally by the loss of neurons.

The mechanism that causes the disease is still not fully understood. One hypothesis is that amyloid plaques are formed by proteolytic cleavage of the larger amyloid precursor protein (APP), a membrane-anchored glycoprotein.

Another hypothesis is that neurofibrillary tangles (NFT) are formed by aggregates of tau protein, a microtubule-associated protein. Protein tau exists as 6 isoforms and hyperphosphorylation is thought to represent the principal cause of tau aggregation into paired helical filaments (PHF) resulting in tauopathy (Billingsley (D9), Woods (D21)). Neurons containing NFTs are to be considered heavily compromised and deemed not to function normally and are believed to finally die.

As will be demonstrated below, the claimed invention is neither novel nor inventive. Additionally, in most aspects it is insufficiently disclosed.

2. The opposed patent was granted with 37 claims. The granted claims can be divided into four classes.

The first class relates to yeast engineered to express tau (*i.e.*, claims 1-21).

The second class relates to the use of such yeasts as a model system (*i.e.*, claims 22-24 and 37).

The third class is directed to methods of screening for compounds that affect the phosphorylation, function, or solubility of tau (*i.e.*, claims 25-34).

The final class of claims relates to methods of identifying the structure-function relation of phosphorylated mutant tau proteins (*i.e.*, claims 35-36).

Claims 1, 22, 23, 24, 25, 32, 34, 35 and 36 recite as follows:

1. An engineered microbial yeast, comprising an introduced nucleotide sequence or an allelic variant, minigene, a synthetic gene or a homologue thereof coding for tau.
22. Use of the engineered microbial yeast of any of the claims 1 to 21 as a model for tau-opathy.

23. Use of the engineered microbial yeast of any of the claims 1 to 21 for in vivo modelling of tau biochemistry.
24. Use of the engineered microbial yeast of any of the claims 1 to 21 as a model for neurodegenerative disorders wherein aberrant phosphorylation and/or function of tau is a characteristic of said neurodegenerative disorders, preferably Alzheimer's disease or frontotemporal dementia with Parkinson's disease.
25. A method of screening a plurality of agents, compounds or chemical signals that directly or indirectly affect tau phosphorylation, function or solubility, comprising a) culturing, growing or suspending the engineered microbial yeast of any of the claims 1 to 21 in an appropriate medium, b) adding a test compound or chemical signal to said engineered microbial yeast or its medium, c) measuring the extent to which said tau phosphorylation, function and/or solubility is affected.
32. A method of screening a plurality of agents, compounds or chemical signals for activity that directly or indirectly modulates tau phosphorylation, function or solubility comprising a) culturing, growing or suspending the engineered microbial yeast of any of the claims 1 to 21 in an appropriate medium, b) adding a test compound or chemical signal to said engineered microbial yeast or its medium, c) detecting or quantitating specified biological or cell morphogenic process in the yeast resulting from said modulation.
34. A method for identifying an antagonist which binds and modulates the activity of an endogenous yeast kinase that modulates phosphorylation of said tau, using the screening method of any of the claims 25 to 33.
35. A method for identifying the structure-function relation of phosphorylated mutant tau proteins, wherein the method involves a) culturing, growing or suspending the engineered microbial yeast of any of the claims 1 to 21, **characterized in that** they express a mutant tau protein and a protein kinase, in an appropriate medium, b) culturing, growing or suspending the engineered microbial yeast of any of the claims 1 to 21, **characterized in that** they express said mutant tau protein but are defective in a gene coding for a protein kinase, in an appropriate medium, c) comparing specified biological processes of said kinase effective and kinase defective engineered microbial yeast.
36. A method for identifying the structure-function relation of phosphorylated mutant tau proteins, wherein the method involves a) culturing, growing or suspending the engineered microbial yeast of any of the claims 1 to 21, **characterized in that** they express a mutant tau protein and a protein phosphatase, in an appropriate medium, b) culturing, growing or suspending the engineered microbial yeast of any of the claims 1 to 21, **characterized in that** they express said mutant tau protein but are defective in a gene coding for a protein phosphatase, in an appropriate medium, c) comparing specified biological processes of said phosphatase effective and phosphatase defective engineered microbial yeast.

Claims dependent on claim 1:

Claim 2 further defines the nucleotide sequence of claim 1 to be from a mammal.

Claim 3 characterizes the tau protein to be a wild type protein isoform, mutant or functional homologue thereof.

Claim 4 requires an endogenous yeast protein kinases or protein phosphatases to exhibit phosphorylation of tau protein.

Claim 5 requires the microbial yeast cell to further comprise a DNA sequence comprising a promoter fused to a yeast kinase or phosphatase that modulates phosphorylation of tau protein.

Likewise, claim 6 requires the microbial yeast cells to further comprise a DNA sequence comprising a promoter fused to a human or mammalian kinase or phosphatase that modulates phosphorylation of tau protein.

Claim 7 requires the microbial yeast cell to further comprise (i) constructs expressing yeast GSK-3 β , any GSK-3 β or a homologous yeast protein and/or (ii) constructs expressing yeast cdk5, any cdk5 or a homologous protein.

Claim 8 characterizes the claimed microbial yeast cell as exhibiting phosphorylation, hyperphosphorylation or dephosphorylation of the tau protein.

Claim 9 requires the claimed microbial yeast cell to comprise one or more further protein kinases or protein phosphatases to be selected from a list.

Claim 10 characterizes the claimed microbial yeast cell to have modified yeast signal-transduction cascade pathways.

Claims 11 and 12 specify that the modulated signal-transduction cascade pathways result in a deletion mutant of an endogenous yeast kinase or phosphatase, preferably a MDS1, PHO85, SCH9 or YAK1 deletion mutant.

Claims 13 and 14 require that the tau protein is expressed under the control of a constitutive or inducible promoter.

Claim 15 requires the tau protein to be fused to a secretion signal and claim 16 requires it to be fused to a reporter protein, while claim 17 specifies that tau drives precipitation of the tau reporter fusion protein, thereby inhibiting or changing the biological function of the reporter protein.

Claim 18 characterizes the claimed microbial yeast cell to comprise a cDNA library derived from human and/or mammalian species including brain tissue.

Claim 19 requires the claimed microbial yeast cell to be further modified either genetically or chemically to facilitate uptake of agents, compounds or chemical signals.

Claim 20 specifies the claimed microbial yeast cell to be of the order to Saccharomycetales, preferably *S. cerevisiae*.

Claim 21 requires that the claimed microbial yeast cell produces wild-type tau, tau isoforms or mutants with phosphorylation status suitable for the purification and/or production thereof.

Claims dependent on claim 23

Claim 37 specifies the tau biochemistry as relating to tau aggregation and/or tau microtubule interaction.

Claim dependent on claim 25

Claim 26 requires the microbial yeast cell applied in the claimed method to be modified either genetically or chemically to facilitate uptake of agents, compounds or chemical signals that affect tau phosphorylation.

Claims 27 and 28 specify a further method step in that the effect of the agents, compounds or clinical signals on the microbial yeast cell is to be compared with the effect of the agents, compounds or clinical signals on a microbial yeast cell that is deficient in the expression of tau or a protein kinase or a protein phosphatase that modulates phosphorylation of tau.

Claim 29 requires the use of antibodies or a Fab thereof in the claimed method which then selectively binds to phosphorylated or unphosphorylated tau.

Claim 30 requires that the agents, compounds or clinical signals applied in the claimed method to bind to and modulate the activity of kinases and phosphatases that modulate phosphorylation of tau.

Claim 31 specifies the protein kinases and protein phosphatases which have to be selected from a list.

Claims dependent on claim 32

Claim 33 further characterizes the biological or cell morphogenic processes referred to in claim 32 to comprise formation of mitotic bundles, pseudo-hyphae, scar-sites, cell size, cell metabolism, cell survival or cell growth.

V. ADDED MATTER: ARTICLE 100(c) EPC IN CONJUNCTION WITH ARTICLE 123(2) EPC

When reading the application as filed of the opposed patent, it is evident that the subject matter of the granted claims finds, apart from a few exceptions, merely support in the original claims. However, none of the granted claims is “mirrored” in the description. Accordingly, the only suitable formal basis for the granted claims is in the original claims.

Yet, some of them have been amended in an inadmissible manner so that the granted claims contain added matter which is detailed below.

1. Claim 6

Granted claim 6 appears to be based on original claims 9 and 13.

Original claim 9 reads as follows:

9) The engineered microbial yeast of any of the claims 1 to 7, which comprises an introduced DNA sequence encoding a promoter, correctly integrated to direct the expression of a human or mammalian kinase, that modulates the phosphorylation of protein tau.

However, granted claim 6 reads as follows:

The engineered microbial yeast of any of claims 1 to 5, which further comprises an introduced DNA sequence encoding a human or mammalian kinase or phosphatase that modulates the phosphorylation of said tau, under control of a promoter sequence.

It is apparent that while original claim 9 reads on a yeast comprising *an introduced DNA sequence encoding a promoter, correctly integrated to direct the expression of a human or mammalian kinase [...]*, granted claim 6 reads on a yeast comprising *an introduced DNA*

sequence encoding a human or mammalian kinase [...] under control of a promoter sequence.

Thus, the wording of original claim 9 has been fundamentally amended, thereby creating new matter which infringes Article 123(2) EPC.

In addition, original claim 13 has been even more fundamentally amended when its subject matter was together with that of original claim 9, combined into granted claim 6.

In fact, original claim 13 reads:

13)The engineered microbial yeast of any of the claims 1 to 7, that further comprises an introduced DNA sequence encoding a promoter, correctly integrated to direct the expression of a yeast phosphatase that modulates the phosphorylation of protein tau.

Firstly, similar to original claim 9, also the wording of original claim 13 was fundamentally amended, thereby infringing Article 123(2) EPC.

Secondly, a “yeast phosphatase” was inadmissibly broadened to any phosphatase. This generalization finds no basis in the application as filed and, thus, offends Article 123(2) EPC.

In sum, granted claim 6 contains added matter.

2. Claim 7

Claim 7 appears to be based on original claims 10 and 11. These claims read as follows:

10)The engineered microbial yeast of any of the claims 1 to 7, that comprises an introduced DNA sequence encoding a promoter, correctly integrated to direct the expression of glycogen synthase kinase-3beta or an homologues protein, that modulates the phosphorylation of protein tau.

11)The engineered microbial yeast of any of the claims 1 to 7, that comprises an introduced DNA sequence encoding a promoter, correctly integrated to direct the expression of cdk5 or an homologue protein, that modulates the phosphorylation of protein tau.

It appears as if original claims 10 and 11 may have been intended to be reflected in the first and third option of granted claim 7 which read as follows:

7. The engineered microbial yeast of any of claims 1 to 6, which further comprises one or more of the following:

- *an introduced DNA sequence comprising a promoter, correctly integrated to direct the expression of a yeast glycogen synthase kinase-3beta or a homologous yeast protein, that modulates the phosphorylation of said tau.*
- *an introduced DNA sequence encoding a glycogen synthase kinase-3beta or a homologous yeast protein, that modulates the phosphorylation of said tau, under control of a promoter sequence.*
- *an introduced DNA sequence comprising a promoter, correctly integrated to direct the expression of a yeast cdk5 or a homologous protein, that modulates the phosphorylation of said tau.*
- *an introduced DNA sequence encoding a cdk5 or a homologous protein, that modulates the phosphorylation of said tau under control of a promoter sequence.*

However, while original claims 10 and 11 do not require the glycogen synthase kinase-3 beta (GSK-3 β) and the cdk5 to be from yeast, the first and third option of granted claim 7 do so.

Hence, while the original claims may provide a basis for a genus kinase and phosphatase, respectively, they do not provide support for a species kinase and phosphatase.

Accordingly, for this reason granted claim 7 contains added matter.

In addition, granted claim 7 contains added matter for another reason. To be more specific, the second and fourth option of granted claim 7 find no basis in the application as filed nor in original claims 10 and 11. Indeed, omitting the feature of the presence of a promoter (cf. original claims 10 and 11) in the introduced DNA sequence is not admissible and, thus, broadens granted claim 7 in an inadmissible manner.

Hence, also for this reason, granted claim 7 contains added matter.

3. Claim 11

Granted claim 11 reads as follows:

The engineered microbial yeast of claim 10, wherein said modulation results in a deletion mutant of an endogenous yeast kinase or phosphatase.

However, this claim does neither find a basis in the specification nor in the original claims.

Should the Proprietor argue that granted claim 11 finds a basis in the Examples, we submit that any extrapolation from the very specific Examples employing *S. cerevisiae* to any yeast constitutes an unallowable generalization, thereby offending Article 123(2) EPC.

To this end, granted claim 11 offends Article 123(2) EPC.

4. Claim 12

Granted claim 12 reads as follows:

The engineered microbial yeast of claim 11, characterized in that said modulation corresponds to the deletion obtained in the MDS1Δ, the PHO85Δ, the SCH9Δ, or the YAK1 deletion mutants

The mere basis for this claim may be found in Examples 2, 4 and 5. However, these Examples are confined to *S. cerevisiae* gene deletions and cannot be extrapolated, *i.e.*, generalized to any yeast.

This unallowable generalization made in granted claim 12 infringes Article 123(2) EPC.

5. Claim 25

Granted claim 25 appears to be based on original claim 53 and reads as follows:

A method of screening a plurality of agents, compounds or chemical signals that directly or indirectly affect tau phosphorylation, function or solubility, comprising a) culturing, growing or suspending the engineered microbial yeast of any of the claims 1 to 21 in an appropriate medium, b) adding a test compound or chemical signal to said engineered microbial yeast or its medium, c) measuring the extent to which said tau phosphorylation, function and/or solubility is affected.

However, original claim 53 reads as follows:

53)A method of screening a plurality of agents, compounds or chemical signals that directly or indirectly affect protein tau phosphorylation, comprising a) culturing, growing or suspending the engineered microbial yeast of any of the claims 1 to 40 in an appropriate medium, b) adding the test compound or chemical signal to said engineered microbial yeast or their medium, c) measuring the extend to which the protein tau or functional homologues thereof are phosphorylated.

It is apparent that step (c) of original claim 53 has been modified from “measuring the extend [sic] to which the protein tau or functional homologues thereof are phosphorylated” to “measuring the extent to which said tau phosphorylation, function and/or solubility is affected.”

There is, however, no basis for this modification in the application as filed.

Hence, granted claim 25 contains added matter.

6. Claim 32

Granted claim 32 reads as follows:

A method of screening a plurality of agents, compounds or chemical signals for activity that directly or indirectly modulates tau phosphorylation, function or solubility comprising a) culturing, growing or suspending the engineered microbial yeast of any of the claims 1 to 21 in an appropriate medium, b) adding a test compound or chemical signal to said engineered microbial yeast or its medium, c) detecting or quantitating specified biological or cell morphogenic process in the yeast resulting from said modulation.

However, nowhere does the application as filed provide formal support for this claim.

Accordingly, granted claim 32 offends Article 123(2) EPC.

7. Claim 34

Granted claim 34 appears to be based on original claim 68.

Granted claim 34 reads as follows:

34. A method for identifying an antagonist which binds and modulates the activity of an endogenous yeast kinase that modulates phosphorylation of said tau, using the screening method of any of the claims 25 to 33.

Original claim 68 reads as follows:

68) A purified antagonist identified using the screening method of any of the claims 53 to 67, which binds and modulates the activity of an endogenous yeast kinase which modulates phosphorylation of said heterologous expressed protein tau or isoforms, mutants or functional homologues.

Apparently, original claim 68 fails to provide support for a method for identifying an antagonist which is the subject matter of granted claim 34.

Thus, granted claim 34 infringes Article 123(2) EPC.

8. Claim 37

Granted claim 37 reads as follows:

37. Use of claim 23 wherein said tau biochemistry relates to tau aggregation and/or tau microtubule interaction.

However, nowhere does the application as filed provide formal support for this claim.

Accordingly, granted claim 37 offends Article 123(2) EPC.

VI. THE CLAIMED SUBJECT MATTER IS NOT ENTITLED TO THE PRIORITY DATE: ARTICLES 87 AND 89 EPC

EP-B1 1 373 529 claims priority of Great Britain application 0104685.3 of February 26, 2001. Opponent considers that the claims of the granted patent lack basis in the priority application and thus, in view of the non-compliance with the requirements of Article 87 EPC, are not entitled to the priority date claimed. Hence, the provisions of Article 89 EPC are not applicable and, therefore, the earliest filing date is the PCT filing date of February 25, 2002.

The priority document of the opposed patent does not contain claims. Yet, while this is not a requirement that the granted claims may be entitled to the priority date, it is a fact which cannot be neglected in the present case.

Indeed, a basis in terms of disclosure for the granted claims can only be found in the original claims of the application as filed. However, these original claims are neither mirrored as such in the priority document nor in the specification thereof.

In fact, as mentioned above, the priority document does not contain claims. Moreover, the specification of the priority document fails to provide support for broadly claimed subject matter of, for example, granted claims 1-4 or 6. Indeed, the priority document may provide for species terms and, thus, species claims, however, it fails to provide a basis for generalizing these species terms and claims. Furthermore, none of the granted claims finds a literal or a direct and unambiguous basis in the priority document.

Hence, the subject matter of the granted claims cannot validly claim the priority date as the effective filing date, but only the filing date. Consequently, prior art that published before the filing date is full prior art and any EP-patent application filed prior to that filing date is relevant prior art pursuant to Article 54(3) EPC; see in this regard the Table in section II, above, which summarizes the documents relied upon in this opposition.

Finally, Opponent reserves the right to contest priority in more detail at a later stage, if the Proprietor will argue that the subject matter of the granted claims can enjoy the priority date.

VII. LACK OF NOVELTY: ARTICLE 100(a) EPC IN CONJUNCTION WITH ARTICLE 54 EPC

1. Claims 1-4, 10, 13-14, 16-17, 19, 20-22, 24-26, and 32-33 are not novel over WO 02/065136 (D14)

Opponent submits that the WO 02/065136 (D14) reference anticipates claims 1-4, 10, 13-14, 16-17, 19, 20-22, 24-26, and 32-33 of the opposed patent for the reasons described below.

D14 was filed on February 15, 2002, and was published on August 22, 2002. **D14** has a priority date of February 15, 2001, which predates the priority date of the opposed patent. Thus, it constitutes prior art under Article 54(3) EPC for the claims of the opposed patent.

For avoidance of doubt, the novelty destroying subject matter of **D14** is entitled to its priority document. Accordingly, we quote from both **D14** and **D14a**.

D14 relates to a yeast based system that can be used to screen for agents that provide therapeutic value for various diseases associated with protein misfolding (see, page 2, bottom, to page 3, top paragraph of **D14** and paragraph bridging pp. 3-4, Table 1, and page 27, lines 19-22 of **D14a**). **D14** teaches that the yeast that

may be employed in the screens include *Saccharomyces cerevisiae* or any other member of *Saccharomycetales* (see, page 7, 5th paragraph and page 14, 2nd paragraph of **D14** and page 9, lines 6-7, and page 15, lines 1-7 of **D14a**).

Among the diseases involving a misfolded protein are tauopathies (see, page 3, lines 7-15 of **D14** and claims 54 and 57 and page 4, line 12 of **D14a**). Tau is specifically listed as a misfolded disease protein encompassed by the invention (see, claims 54, 57 and 58; Table 1, line 51 of **D14**; and page 9, lines 16-19 of **D14a**).

The invention in **D14** is based on the observation that proteins such as tau that misfold and are associated with a disease ("misfolded protein response") can be expressed in yeast as the basis for screening for therapeutic agents for the treatment of a disease such as a tauopathy (see, page 4, lines 17-22 of **D14** and page 4, lines 18-20 of **D14a**). The screen uses viability of the yeast which expresses a misfolded disease protein as a read out to identify compounds that have therapeutic potential in treatment of diseases associated with the misfolded protein (see, page 2, lines 27-30 of **D14** and page 4, lines 28-29 of **D14a**).

D14 also discloses use of wild type (see, page 26, 4th paragraph and page 27, 3rd paragraph of **D14** and page 27, lines 26-27 and page 28, lines 28-31 of **D14a**), allelic variants (see, page 26, 4th paragraph and page 27, 3rd paragraph of **D14** and paragraph bridging pages 28-29 of **D14a**), mutants (see, page 26, 4th paragraph; page 27, 3rd paragraph and page 28, last paragraph of **D14** and page 27, lines 3-12; paragraph bridging pages 28-29; pages 49-51 of **D14a**), and reporter fusion proteins (see, page 38, bottom to page 39, top paragraph and page 48, 1st paragraph of **D14** and paragraph bridging pages 41-42; page 52, lines 2-17; and Figures 2 and 3 of **D14a**). In addition, **D14** teaches the use of inducible and constitutive promoters (see, paragraph bridging pages 33 and 34 and page 34, 3rd paragraph of **D14** and paragraph bridging pages 36-37 of **D14a**) as well as episomal and integrating plasmids (see, page 30, 3rd paragraph to page 31, 4th paragraph of **D14** and page 32, line 18 to page 34, line 13 of **D14a**). **D14** also teaches the aggregation of reporter fusions (see, page 51, 2nd paragraph of **D14** and page 55, line 28 to page 56, line 10 of **D14a**). **D14** also discloses the use of yeast having modified signal transduction pathways as a result of mutations in heat shock protein genes (see, page 18, lines 25-32).

In sum, **D14** teaches the subject matter of claims 1-4, 10, 13-14, 16-17, 19, 20-22, 24-26, and 32-33 of the opposed patent and thereby is novelty destroying for these claims.

2. **Claims 1-4, 6-8, 10, 13, 16, and 20-21 are not novel over Cafferty (D15)**

Opponent submits that the Cafferty (D15) reference anticipates claim 1-4, 6-8, 10, 13, 16, and 20-21 of the opposed patent for the reasons described below.

D15 was presented in August 2000, and thus is prior art under Article 54(2) EPC for the claims of the opposed patent.

D15 teaches pAS2-1 and pACT expression vectors that express GSK-3 β and tau (see, "Construction of expression plasmids," pages 10-14). The pAS2-1 vector contains the GAL4 DNA binding domain and the pACT vector contains the GAL4 activation domain. Both vectors regulate gene expression via the *ADH1* constitutive promoter. **D15** also teaches yeast cells (*e.g.*, *Saccharomyces cerevisiae*) (see, page 14) transformed with expression vectors that express GSK-3 β and tau and which produce these proteins (see, pages 22-24; Fig. 11 (pages 38-39); and Fig. 13 (pages 40-41)).

Thus, this reference teaches yeasts expressing tau (subject matter of claims 1-3); yeasts expressing tau and a mammalian kinase (*i.e.*, GSK-3 β) (subject matter of claims 6-7); tau expressed from a constitutive promoter (subject matter of claim 13); tau coupled in frame to a reporter protein (GAL4 DNA binding domain or activation domain) (subject matter of claim 16); the yeast strain *Saccharomyces cerevisiae* (subject matter of claim 20); and yeasts producing tau (subject matter of claim 21). It is noted with respect to claims 4 and 8 that it is expected that tau produced in yeast would inherently be phosphorylated or dephosphorylated, in the absence of evidence to the contrary.

Accordingly, **D15** anticipates claims 1-4, 6-8, 10, 13, and 20-21 of the opposed patent.

3. **Claims 1-4, 13-14, and 20-21 are not novel over US 5,492,812 (D11) or WO 93/03369 (D12)**

Opponent submits that the US 5,492,812 (**D11**) or WO 93/03369 (**D12**) reference anticipates claim 1-4, 13-14, and 20-21 of the opposed patent for the reasons described below.

D12 was published on February 18, 1993, a date which predates the priority date of the opposed patent, and thus is also prior art under Article 54(2) EPC for the claims of the opposed patent. **D11** was published on February 20, 1996, a date which also predates the priority date of the opposed patent, and thus is prior art under Article 54(2) EPC for the claims of the opposed patent.

D11 discloses a variety of host-expression systems that can be used to express tau-proteins or fragments thereof. These systems are described at column 9, line 47 to column 10, line 39; column 11, lines 4-49; and column 12, lines 22-26 under the section entitled "Cloning and Expression of Recombinant Tau-Proteins and/or Tau-Peptides." (also see, **D12**, page 17, line 1 to page 23, line 28).

In particular, **D11** teaches that:

A variety of host-expression vector systems may be utilized to express tau-proteins or fragments thereof. These include, but are not limited to microorganisms such as . . . yeast transformed with recombinant yeast expression vectors containing a coding sequence for a tau-protein or fragment thereof . . . (see, col. 9, ll. 48-50 and 54-56; emphasis added).

In addition, **D11** teaches that:

The expression elements of these vectors vary in their strength and specificities. Depending on the host/vector system utilized, any of a number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used in the expression vector. (see, col. 9, ll. 63-67; emphasis added).

. . . In yeast, a number of vectors containing constitutive or inducible promoters may be used. . . For complementation assays in yeast, cDNAs for tau-proteins or fragments thereof may be cloned into yeast episomal plasmids (YEp) which replicate autonomously in yeast due to the presence of the yeast 2m circle. The tau-protein or fragment thereof sequence may be cloned behind either a constitutive yeast promoter such as ADH or LEU2 or an inducible promoter such as GAL. . . Yep plasmids transform at high efficiency and the plasmids are extremely stable. Alternatively, vectors may be used which promote integration of foreign DNA sequences into the yeast chromosome. (see, col. 10, ll. 11-12; 24-31; and 36-39; emphasis added).

Further, **D11** teaches that:

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. . . Furthermore, modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristics and specific mechanisms for the post translational processing and modification of proteins. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. (see, col. 11, ll. 23-26 and 32-39; emphasis added).

Therefore, as evidenced by **D11** or **D12**, at the time of the filing of the opposed patent, persons of ordinary skill in the art had already been taught:

- the subject matter of claim 1 of the opposed patent – i.e., an engineered yeast comprising an introduced nucleic acid sequence coding for tau (e.g., column 9, lines 54-56);

- the subject matter of claim 2 of the opposed patent – *i.e.*, the yeast cell of claim 1 comprising a mammalian (human) nucleotide sequence coding for tau (*e.g.*, Fig. 1 - SEQ ID NO:1; column 6, lines 39-42);
- the subject matter of claim 3 of the opposed patent – *i.e.*, the yeast cell of claim 1 comprising a wild type protein tau or a mutant thereof (*e.g.*, column 9, lines 54-56);
- the subject matter of claim 4 of the opposed patent – *i.e.*, the yeast cell of claim 1, wherein endogenous yeast protein kinases or phosphatases modulate phosphorylation of said tau. It is noted that phosphorylation or dephosphorylation of tau in yeast by endogenous yeast protein kinases or phosphatases is inherent to a yeast cell that is transformed with, or that has an integrated tau protein or fragment thereof, absent evidence to the contrary;
- the subject matter of claims 13 and 14 of the opposed patent – *i.e.*, an engineered yeast wherein tau is expressed using a constitutive or inducible promoter (*e.g.*, column 10, lines 28-33);
- the subject matter of claim 20 of the opposed patent – *i.e.*, an engineered yeast wherein the yeast is of the order Saccharomycetales (*e.g.*, column 10, lines 12-31); and
- the subject matter of claim 21 of the opposed patent – *i.e.*, yeast producing tau proteins with desired phosphorylation status for purification (*e.g.*, section entitled “Cloning and Expression of Recombinant Tau-Proteins and/or Tau-Peptides,” column 10, lines 9-67, and col. 11, ll. 23-26 and 32-39).

Thus, Opponent submits that claims 1-4, 13-14 and 20-21 lack novelty over **D11** or **D12**.

4. Claims 1-4 and 18 are not novel over WO 99/62548 (D16)

Opponent submits that the WO 99/62548 (D16) reference anticipates claims 1-4 and 18 of the opposed patent for the reasons described below.

D16, was published on December 9, 1999, *i.e.*, prior to the priority date of the opposed patent, and therefore is prior art under Article 54(2) EPC for the claims of the opposed patent.

D16 is directed to methods and compositions for the diagnosis, modeling, and treatment of tau-related pathologies.

D16 teaches:

In screening for modulators of tauopathy, one of skill in the art can employ the two hybrid system to look for proteins that bind to tau. Using a bait system of yeast and cDNA libraries, proteins that bind to tau can be fished out. Such techniques

are well known to those of skill in the art and are described in e.g., U.S. Pat. No. 5,525,490; U.S. patent, Chien et al., 1991; Fields et al., 1994, each incorporated herein by reference). Also it may be important to examine phosphorylation proteins (kinases) specific to tau since the abnormal tau is hyperphosphorylated. U.S. Pat. No. 5,601,985, incorporated herein by reference, relates to a method of diagnosing a disease associated with the accumulation of paired helical filaments by identifying the presence of an abnormally phosphorylated tau, as such the techniques described will be useful in the present invention. (see, page 38, first paragraph; emphasis added).

Accordingly, **D16** teaches an engineered yeast comprising a nucleotide sequence coding for tau. The reference teaches mammalian tau and tau isoforms. The subject matter of claim 4 is inherently anticipated as tau expressed in yeast is expected to be phosphorylated/dephosphorylated by endogenous kinases/phosphatases. **D16** also teaches the subject matter of claim 18 by teaching the use of cDNA libraries for, e.g., to identify tau-specific kinases.

Thus, **D16** anticipates the subject of claims 1-4 and 18.

5. Claims 1-4 and 20 are not novel over WO 02/35237 (D17)

Opponent submits that the WO 02/35237 (D17) reference anticipates claims 1-4 and 20 of the opposed patent for the reasons described below.

D17 was published on May 2, 2002, and was filed on October 22, 2001. It has a priority date of October 24, 2000, a date which predates the priority date of the opposed patent. Thus, **D17** is prior art at least under Article 54(3) EPC for the claims of the opposed patent.

For avoidance of doubt, the novelty destroying subject matter of **D17** is also present in its priority document **D17a**. Accordingly, we quote from both **D17** and **D17a**.

D17 discloses methods for the *in vivo* identification of intracellular epitopes. Specifically, it discloses the use of tau mutants to identify antibodies (see, page 4, bottom, to page 5, top paragraph; page 6, lines 3-6; page 6, line 19 to page 7, line 16 of **D17** and page 5, lines 7-16; page 6, lines 13-14; pages 6 and 7, bridging paragraph of **D17a**). This reference discloses, as a preferred embodiment, the use of yeast cells (e.g., L40) (see, page 6, lines 1-2 and page 7, last paragraph of **D17** and page 6, lines 13-14; page 7, last paragraph of **D17a**). L40 cells are a *Saccharomyces cerevisiae* strain.

Thus, **D17** discloses yeasts expressing tau. Accordingly, Opponent submits that claims 1-4 and 20 lack novelty over **D17**.

VIII. LACK OF INVENTIVE STEP: ARTICLE 100(a) EPC IN CONJUNCTION WITH ARTICLE 56 EPC

As demonstrated in section VII, above, most of the claims of the opposed patent are devoid of novelty. It goes without saying, that these claims as well as the remainder of the claims also lack inventive step over the documents referred to in section VII, above.

Of course, Opponent reserves the right to provide arguments on inventive step in more detail at a later stage and refers to the Headnotes of T 131/01:

"In a case where a patent has been opposed under Article 100(a) EPC on the grounds of lack of novelty and inventive step having regard to a prior art document, and the ground of lack of novelty has been substantiated pursuant to Rule 55(c), a specific substantiation of the ground of lack of inventive step is neither necessary - given that novelty is a prerequisite for determining whether an invention involves an inventive step and such prerequisite is allegedly not satisfied - nor generally possible without contradicting the reasoning presented in support of lack of novelty."

IX. INSUFFICIENT DISCLOSURE ARTICLE 100(b) EPC IN CONJUNCTION WITH ARTICLE 83 EPC

According to Article 83 EPC, the invention must be sufficiently disclosed, which requires that the teaching of the application enables the skilled person to carry out the whole subject matter which is defined in the claims without undue burden.

Furthermore, it is an established principle developed by the Boards of Appeal that it is a reasonable principle of patent law that the extent of monopoly conferred by a patent should correspond to, and be justified by, the technical contribution to the art.

The opposed patent, however, seeks protection for a monopoly which is not justified by its insufficiently disclosed technical contribution as will be shown in the following.

1. Claim 4

Claim 4 broadly recites "yeast protein kinases and . . . phosphatases;" however, the disclosure provides only one phosphatase and a few kinases.

Specifically, the opposed patent, at best, provides limited guidance on yeast kinases (*i.e.*, Mds1, Pho85, PKA, Sch9, Yak1) that are allegedly capable of phosphorylating human tau40 protein; see Examples 2 and 5.

It is also noted that the opposed patent only teaches that the *S. cerevisiae* PPH21 phosphatase is allegedly capable of dephosphorylating human tau40 protein; see Example 3.

2. Claim 5

Claim 5 broadly recites “yeast protein kinase or phosphatase;” however, the disclosure provides only one phosphatase and a few kinases.

Thus, for the same reasons as to why claim 4 is insufficiently disclosed, also claim 5 is insufficiently disclosed.

3. Claim 6

Claim 6 broadly recites “mammalian kinase or phosphatase;” however, the disclosure provides no representative species of mammalian kinases or phosphatases.

In fact, the opposed patent may merely support that human GSK-3 β kinase works; see Example 4. However, the opposed patent fails to provide experimental evidence for any mammalian phosphatase at all.

Accordingly, claim 6 is insufficiently disclosed for a mammalian kinase and a mammalian phosphatase which modulates the phosphorylation of tau in an engineered microbial yeast.

4. Claim 7

Claim 7, *inter alia*, recites that the yeast comprises and presumably expresses any GSK-3 β and/or any cdk5 or a homologous yeast protein thereof. However, as explained above only limited guidance on yeast kinases and only PPH21 phosphatase have been used in the Examples.

Hence, claim 7 as regards a microbial yeast comprising and expressing any GSK-3 β and/or any phosphatase as well as any yeast phosphatase, let alone homologous proteins thereof, is insufficiently disclosed as evidenced by the opposed patent itself.

5. Claim 8

Claim 8 recites that the microbial yeast when cultured exhibits, *inter alia*, hyperphosphorylation of tau.

However, the opposed patent fails to demonstrate that the claimed microbial yeast is capable of hyperphosphorylating tau. It, thus, amounts to undue burden for the skilled person to provide a yeast exhibiting hyperphosphorylation of tau. Furthermore, it is an undue burden to find the conditions under which tau is hyperphosphorylated in yeast.

Hence, claim 8 as regards hyperphosphorylation of tau is insufficiently disclosed.

6. Claim 9

Claim 9 requires the microbial yeast cell to comprise and presumably to express further kinases or phosphatases. However, the opposed patent fails to provide technical support for many of the specific kinases and phosphatases to have an effect on tau.

Thus, claim 9 is insufficiently disclosed.

7. Claims 10 and 11

Claims 10 and 11 require the microbial yeast to be modulated to have modified yeast signal transduction cascade pathways, preferably resulting in a deletion mutant of an endogenous yeast kinase or phosphatase.

However, the skilled person is left with guessing as to which yeast signal transduction cascade pathways should be modified. Hence, claim 10 is insufficiently disclosed.

Although claim 11 provides some guidance that an endogenous yeast kinase or phosphatase is to be deleted, the skilled person is again left with guessing as to which yeast kinase or phosphatase is to be deleted.

In particular, with respect to a yeast phosphatase, the opposed patent demonstrates that only PPH21, if over-expressed, has an effect on tau. This feature is not present in claim 11.

In claim 11, the recitation "wherein said modulation results in a deletion mutant of an endogenous yeast kinase or phosphatase" leaves the skilled person in doubt because it is not understood how modulation "results in" a deletion mutant.

Hence, because of the foregoing reasons, claim 11 is insufficiently disclosed.

8. Claim 15

In claim 15, the purpose of fusing tau to a secretion signal is unclear. Tau is a cytoplasmic protein that is modulated by cytoplasmic kinases/phosphatases.

9. Claim 17

Claim 17 requires that tau drives the precipitation of a tau reporter fusion protein, thereby inhibiting or changing the biological function of the reporter protein.

However, claim 17 is a mere desideratum claim, since the skilled person would not know as to how tau should “drive” the precipitation of a tau reporter fusion protein so that it inhibits or changes the biological function of the reporter protein.

What does “drives the precipitation” mean? What biological function of which reporter protein should be inhibited or even changed?

In sum, the skilled person is left with guessing as to how s/he should put the subject matter of claim 17 into practice. Moreover, the specification is silent about precipitation of tau, inhibition or change of biological function of a reporter protein etc.

In essence, claim 17 is insufficiently disclosed.

10. Claims 19, 25-28 and 30-32

Claims 19, 25-28 and 30-32 are insufficiently disclosed, since the skilled person is left with guessing as to what constitutes a “chemical signal”. This term is so vague that it places an undue burden on the skilled person in finding out what is meant by this term. Hence, the skilled person would have to perform undue experimentation to identify a “chemical signal” that is monitored (claim 19) or screened (claims 25-28 and 30-32).

Accordingly, claims 19, 25-28 and 30-32 are insufficiently disclosed.

11. Claim 21

Claim 21 requires that the claimed yeast produces tau proteins with phosphorylation status suitable for the purification and/or production thereof. However, the term “suitable

for” is so vague that the skilled person cannot understand what phosphorylation status makes a tau protein suitable for purification and/or production.

Hence, claim 21 is insufficiently disclosed.

12. **Claims 23 and 37**

Claim 23 broadly recites “tau biochemistry,” however, it only discloses phosphorylation, sensitivity to benomyl, effect on pseudohyphae formation, and solubility.

Thus, the skilled person cannot reduce the claimed use to practice without undue experimentation to find out what is meant by “tau biochemistry”.

Similarly, the skilled person cannot reduce tau aggregation and/or tau microtubule interaction into practice as is required by claim 37, since the opposed patent fails to provide any evidence that human tau40 aggregates and/or affects yeast microtubule aggregation.

Accordingly, claims 23 and 37 are insufficiently disclosed.

13. **Claim 31**

For the same reasons as to why claim 9 is insufficiently disclosed, claim 31 is so, too; see item 9, above.

14. **Claim 33**

Claim 33 specifies the biological or all morphogenic processes applied in the screening method of claim 32 to be the formation of mitotic bundles, formation of pseudo-hyphae, formation of scar-sites, cell-size, cell metabolism, cell survival or cell growth in defined conditions.

However, the opposed patent fails to demonstrate an effect of the allegedly expressed tau protein or the formation of mitotic bundles or formation of scar-sites, let alone such an effect under defined conditions. Hence, it is up to the skilled person to find out as to whether expression of tau has any of these effects in yeast cells under defined conditions. As regards defined conditions, it is also up to the skilled person to find out what are defined conditions.

It follows that claim 33 is insufficiently disclosed.

15. Claim 34

Claim 34 requires that an antagonist binds and modulates the activity of an endogenous yeast kinase that modulates phosphorylation of tau.

However, as explained in item 4, above, only limited guidance as to kinases that may modulate tau phosphorylation in *S. cerevisiae* is *provided*. Thus, for the same reasons as to why claim 4 is insufficiently disclosed, claim 34 is so, too.

16. Claims 35 and 36

In the method of claims 35 and 36 yeast cells are required to either express or to not express “a protein kinase” or “a protein phosphatase”. However, the skilled person is left with guessing as to which protein kinase or protein phosphatase s/he should express in a yeast cell.

As explained above, only limited guidance is provided as to which protein kinases phosphorylate a human tau40 protein in *S. cerevisiae*. Likewise, the only protein phosphatase that may work, but only if over-expressed, insofar as it then dephosphorylates human tau40 protein is PPH21 of *S. cerevisiae*.

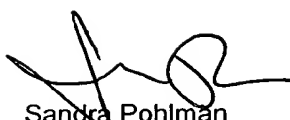
Hence, claims 35 and 36 are overly broad and, thus, not enabled over their entire breadth.

Consequently, claims 35 and 36 are insufficiently disclosed.

X. SUMMARY

Considering the above-presented facts, evidence and arguments, we have demonstrated that the granted claims contain added matter, lack novelty, inventive step and are insufficiently disclosed.

Hence, our request for revocation of the patent in its entirety is fully justified.



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Enclosures:

Documents **D1-D30**

Copy of the original application

Copy of the priority document